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PATENT
Our Docket: P31 8929
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Geoffrey M. Wahl
Stephen V. O'Gorman

Serial No.: 07/666,252

Filed: March 8, 1991

For: FLP-MEDIATED GENE MODIFICATION IN MAMMALIAN CELLS, AND COMPOSITIONS AND CELLS USEFUL THEREFOR

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D. C. 20231, on 6/19/91
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Date of Signature

Honorable Commissioner of
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Washington, D.C. 20231

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INFORMATION DISCLOSURE STATEMENT

Sir:

In accordance with 37.C.F.R. 1.97, enclosed are references relating to the above-identified application. For the convenience of the Examiner, these references are listed on the attached Form PTO-1449 and a copy of each is enclosed herewith.

U.S. 4,959,317 (assigned to E.I. DuPont de Nemours and Company, issued September 25, 1990). Relates to a method for producing site-specific recombination of DNA in eukaryotic cells employing DNA sequences comprising first and second lox sites and Cre (a recombinase which effects site-specific recombination of DNA at lox sites).

European Patent Application 220,009 (Applicant -- E.I. DuPont de Nemours and Company, published April 29, 1987). Publication based on the parent of U.S. 4,959,317. Relates to a method for producing site-specific recombination of DNA in yeast using the lox-Cre recombination system.

European Patent Application 245,481 (see P.C.T. No. 8703006 (Applicant Genetics Institute Incorporated, published May 21, 1987). Describes processes for increasing the rate of production of carbon dioxide, ethanol, and other fermentation products produced by yeast. The use of the recombinase, FLP, is discussed, beginning at page 13, six lines up from the bottom continuing through page 19.

European Patent Application 286,424 (Applicant -- Delta Biotechnology Limited, published October 12, 1988). Describes a two micron plasmid vector comprising a DNA sequence which is intended to be lost by recombination, three two micron FLP recombination sites, of which one pair of sites is in direct orientation and the other two pairs are in indirect orientation and a DNA sequence coding for a protein or peptide of interest, the sequence to be lost being located between the sites which are in direct orientation.

European Patent Application 300,422 (Applicant -- E.I. DuPont de Nemours and Company, published January 25, 1989). Provides methods for applying the Cre-lox recombination system to the preparation of stable and viable recombinant animal cell viral vectors.

Sauer and Henderson, "Site-specific DNA recombination in mammalian cells by the Cre recombinase of bacteriophage P1", in Proc. Natl. Acad. Sci. USA Vol. 85:5166-5170 (1988). Describes the use of the Cre protein (encoded by the coliphage P1) to promote site-specific recombination in a mammalian cell line.

Sauer and Henderson, "Cre-stimulated recombination at loxP-containing DNA sequences placed into the mammalian genome", in Nucleic Acids Research, Vol. 17:147-161 (1989). Shows that the Cre recombinase of coliphage P1 is capable of recognizing chromosomal loxP sites placed into a mammalian genome to cause recombination at those loxP sites.

Sauer and Henderson, "Targeted Insertion of Exogenous DNA into the Eukaryotic Genome by the Cre Recombinase", in The New Biologist, Vol. 2:441-449 (1990). Examines the ability of Cre to perform integrative recombination in eukaryotic cells.

Huang and Gorman, "Intervening sequences increase efficiency of RNA 3' processing and accumulation of cytoplasmic RNA", in Nucleic Acids Research, Vol. 18: 937-947 (1990). Background reference containing detail as to the source of some DNA used in the experimental section of the present application. See especially plasmid pMLSIS.CAT, discussed at page 940.

Golic and Lindquist, "The FLP Recombinase of Yeast Catalyzes Site-Specific Recombination in the Drosophila Genome", in Cell, Vol. 59:499-509 (1989). Describes the development of inducible site-specific recombination systems for use in Drosophila melanogaster.

Casadaban et al., "ß-Galactosidase Gene Fusions for Analyzing Gene Expression in Escherichia coli and Yeast", in Methods in Enzymology, Vol. 100:293-308 (1983). Background reference which describes the ß-galactosidase-encoding vector pSKS105 (see page 301).

Broach and Hicks, "Replication and Recombination Functions Associated with the Yeast Plasmid, 2μ Circle", in Cell, Vol. 21:501-508 (1980). Background reference which discloses the presence of a product produced by S. cerevisiae 2μ circle which is necessary for normal mitotic recombination in yeast. This product is designated as FLP.

Jayaram, "Two-micrometer circle site-specific recombination: the minimal substrate and the possible role of flanking sequences" in Proc. Natl. Acad. Sci. USA, Vol. 82:5875-5879 (1985). Describes the use of chemically synthesized FLP substrates to determine what sequences constitute the "minimal" FLP site, what DNA symmetries are germane to the reaction, and whether the 2-μm circle sequences flanking the minimal site can influence its reactivity. The sequence of the synthetic FLP substrate, J_3, is presented in column 1 at page 5876; and the sequence of the FLP recombination region is presented at column 1 of page 5878.

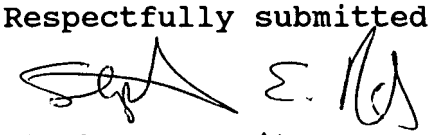
Utatsu et al., "Yeast Plasmids Resembling 2μm DNA: Regional Similarities and Diversities at the Molecular Level" in Journal of Bacteriology, Vol. 169:5537-5545 (1987). Describes structural analyses of two plasmids derived from Zygosaccharomyces species and comparative studies of the functional genes of various yeast derived plasmids resembling 2μm DNA of Saccharomyces cerevisiae.

Sauer, "Functional Expression of the cre-lox Site-Specific Recombination System in the Yeast Saccharomyces cerevisiae" in Molecular and Cellular Biology, Vol. 7:2087-2096 (1987). Demonstrates the ability of the procaryotic cre-lox recombination system of coliphage P1 to function in a eucaryote, the yeast Saccharomyces cerevisiae.

Senecoff et al., "DNA Recognition by the FLP Recombinase of the Yeast 2 μ Plasmid", in J. Med. Biol., Vol. 201:405-421 (1988). Background reference describing a mutational analysis of the FLP binding site.

It is respectfully requested that these references be considered in the examination of this application and their consideration be made of written record in the application file.

Respectfully submitted,



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